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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/226,895	01/07/1999	MICHAEL ROSENBLUM	D6205	8983

7590 09/25/2006

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EXAMINER

CANELLA, KAREN A

ART UNIT PAPER NUMBER

1643

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/226,895

Applicant(s)

ROSENBLUM ET AL

Examiner

Karen A. Canella

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 5,6,8,9 and 11-13 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 5,8,9,12 and 133 is/are rejected.
- 7) ☐ Claim(s) 6, 11 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Claims 1-4, 7, 10, 14 and 15 are canceled. Claims 5, 6, 8, 11 and 12 are amended.
Claims 5, 6, 8, 9 and 11-13 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 5, 8, 9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mehta et al (Proceed Amer Assoc Cancer Res, 1997, Vol. 38, page 88, cited in a previous Office action) in view of O'Connor et al (Blood, Vol. 86, pp. 4286-4294).

Claim 12 is drawn to a method of treating an individual having a drug-resistant leukemia comprising administering to said individual a pharmacologically effective dose of a retinoid which up-regulates the expression of CD38 antigen, and administering to the same individual a pharmacologically effective dose of an immunotoxin directed against CD38 antigen. Claim 13 embodies the method of claim 12 wherein the drug-resistant leukemia is adriamycin-resistant leukemia. Claim 5 embodies the method of claim 12 wherein said retinoid is selected from a group including ATRA and 9-cis-RA. Claim 8 embodies the method of claim 12 wherein said immunotoxin comprises a monoclonal antibody directed against the CD38 antigen conjugated to a toxin. Claim 9 specifies that the toxin is gelonin.

Mehta et al teach that retinoic acid increases the expression of CD38 on leukemia cells *ex vivo* and leukemia cell lines. Mehta et al teach that retinoic acid treatment of leukemia cell lines increase the toxicity of an anti-CD38 gelonin immunotoxin. Mehta et al do not teach the actual administration of anti-CD38 gelonin immunotoxin to patients with leukemia or drug resistant leukemia.

O'Connor et al teach that drug resistance in tumors can be overcome by treating with agents which have different mechanisms of action which are still effective in the drug resistant tumor cells. O'Connor et al suggest that an immunotoxin binding to a receptor followed by internalization and delivery of the toxic portion to inactivate ribosomes in the cytoplasm is not a toxic mechanism common to chemotherapeutic drugs current in use (page 4286, second column, lines 3-14).

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It would have been prima facie obvious at the time the claimed invention was made to administer the anti-CD38 gelonin immunotoxin in combination with retinoic acid to patients having drug resistant leukemia or adriamycin-resistant leukemia. One of skill in the art would have been motivated to do so by the teachings of O'Connor on the efficacy of providing an immunotoxin which exerts toxicity through internalization and inactivation of ribosomes in the cytoplasm. One of skill in the art would expect that the retinoic acid would increase the likelihood of an immunotoxin molecule to bind to a target cell because the target cell would express more CD38 due to treatment with the retinoic acid. One of skill in the art would expect that an individual having leukemia cells which were resistant to adriamycin would be sensitive to an immunotoxin comprising gelonin because O'Connor et al teach that ribosomal toxicity is not common to the chemotherapeutic drugs in current use which include adriamycin. It is noted that the generic recitation of retinoic acid in Mehta et al fulfills the specific embodiment of claim 5 which includes both cis and trans retinoic acid.

Applicant argues that Mehta teaches that retinoic acid failed to increase the level of CD38 on the drug-resistant HL-60 cells of Mehta et al. This has been considered but not found persuasive. Mehta states that pretreatment of the leukemia cells with retinoic acid caused an increase in killing by the immunotoxin, but that normal granulocytes that lacked basal expression of CD38 could not be induced to express CD38 antigen following RA treatment.

Applicant has provided two citations that purported teach that HL-60 resistant leukemia cells are not able to upregulate CD38 in response to retinoic acid. Upon review of both of the Notarbartolo et al reference and the Terashi et al reference it is noted that no mention is made of the effect of retinoic acid on HL-60 cells. Further, even in the event that the references did teach that the HL-60 R leukemia cells did not upregulate CD38 in response to retinoic acid, this would be unpersuasive, because said references were published after the effective filing date. The analysis for obviousness is necessarily what was obvious to one of skill in the art at the time of filing (M.P.E.P., section 2141.01 "III. CONTENT OF THE PRIOR ART IS DETERMINED AT THE TIME THE INVENTION WAS MADE").

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicant's amendments.

Claims 6 and 11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

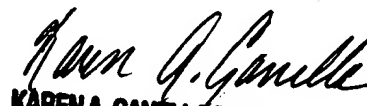
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.

9/17/2006


KARENA. CANELLA PH.D.
PRIMARY EXAMINER